II. REMARKS

Formal Matters

Claims 1-9, 15, and 17-19 are pending after entry of the amendments set forth herein.

Claims 1-9 and 15-19 were examined and were rejected. Claim 16 was objected to.

Claims 1 and 5 are amended. The amendments to the claims were made solely in the interest of expediting prosecution, and are not to be construed as acquiescence to any objection or rejection of any claim. The amendments to claim 1 are editorial in nature. Support for the amendment to claim 5 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: paragraph 0058. Accordingly, no new matter is added by these amendments.

Claim 16 is canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Withdrawal of previous rejections

Applicants note with gratitude that the following rejections, raised in the August 25, 2005 Office Action, have been withdrawn: 1) rejection of claims 1-8 and 15-18 under 35 U.S.C.§103(a); and 2) rejection of claim 9 under 35 U.S.C.§103(a).

Claim objection

Claim 16 was objected to as being a substantial duplicate of claim 2.

Claim 16 is canceled without prejudice to renewal.

Rejection under 35 U.S.C.§112, first paragraph

Claims 1-9 and 15-19 were rejected under 35 U.S.C.§112, first paragraph, as allegedly failing to comply with the enablement requirement.

The Office Action stated that: 1) Applicants' specification does not describe the exact experimental conditions for performing the claimed two-step method, comprising modifying SDMA and arginine, followed by detecting ADMA in the sample; 2) Applicants' specification does not describe the

exact reaction conditions for reacting a sample with an α-dicarbonyl compound, resulting in detectable ADMA; 3) Applicants' specification does not describe a detecting means capable of detecting AMDA in the product of a reaction between a sample and an α-dicarbonyl compound; and 4) other than phenylglyoxal derivatives, Applicant's specification does not contemplate any other modified SDMA derivatives or modified arginine derivatives. Applicants respectfully traverse the rejection.

Comments regarding the instant invention as claimed.

As discussed in the instant specification, elevated asymmetric dimethylarginine (ADMA) levels have been observed in various conditions, such as hypertension, and elevated ADMA levels are also associated with an increased risk of cardiovascular disease. Currently available methods of detecting ADMA in biological samples are laborious. High pressure liquid chromatography (HPLC) is the most commonly used method to quantify ADMA. One reason for the difficulty in detecting ADMA is the difficulty in distinguishing ADMA from symmetric dimethylarginine (SDMA) and arginine.

The present inventors have developed a method of detecting ADMA in a sample that comprises, in addition to ADMA, SDMA and/or arginine. SDMA and arginine react with an α-dicarbonyl compound, but ADMA does not. The α-dicarbonyl compound modifies SDMA and arginine, but not the ADMA. While it is difficult to distinguish SDMA from ADMA, modified SDMA is readily distinguishable from ADMA, and the same is true for arginine. Thus, modifying any SDMA and arginine that may be present in the sample provides a means for detecting ADMA without interference from SDMA or arginine.

The specification provides ample description of the claimed method.

The Office Action stated that the specification does not describe the exact experimental conditions for performing the claimed two-step method, comprising modifying SDMA and arginine, followed by detecting ADMA in the sample. However, the instant specification provides ample description of experimental conditions for performing the claimed method, involving contacting a sample with an α-dicarbonyl compound, to produce modified ADMA and modified arginine, and detecting ADMA. The specification provides a list of suitable α-dicarbonyl compounds in paragraphs 0030 and 0031. The specification describes suitable concentrations of the α-dicarbonyl compound. Specification, paragraph 0034. The specification provides reaction times and temperatures for the reaction between the α-dicarbonyl compound and the SDMA and/or arginine. Specification, paragraphs 0035 and 0038. Exemplary reaction conditions are also described. Specification, paragraph 0099.

Thus, given the guidance in the specification, those skilled in the art could readily carry out a method as claimed.

The Office Action stated that claim 1 "does not specify whether/what sample clean-up steps may be required." However, sample clean up is not necessarily required to perform the claimed method. The claimed method does not relate to purifying ADMA, but to detecting ADMA. As long as the measured compound (ADMA) is unaltered, the possible presence of impurities in the reaction is irrelevant.

The specification provides ample description of methods for detecting ADMA.

The Office Action stated that the specification does not describe a detecting means capable of detecting AMDA. However, the specification provides ample description of how to detect ADMA. The methods include converting ADMA to citrulline, followed by spectrophotometric detection of citrulline; detecting ADMA with an antibody that binds dimethylarginines; HPLC; and capillary electrophoresis. Specification, paragraph 0043. HPLC methods are described in detail. Specification, paragraphs 0044-0051. Capillary electrophoresis methods were known in the art, as indicated in the specification. Specification, paragraph 0053. Immunoassays are also described. Specification, paragraphs 0054-0065. Thus, given the guidance in the specification, those skilled in the art could readily carry out a method as claimed.

The specification contemplates use of any of a variety of α-dicarbonyl compounds.

The Office Action stated that, other than phenylglyoxal derivatives, Applicant's specification does not contemplate any other modified SDMA derivatives or modified arginine derivatives. This is not correct. As noted above, the specification provides a list of suitable α-dicarbonyl compounds in paragraphs 0030 and 0031. Phenylglyoxal is but one example of a suitable α-dicarbonyl compound that can be used.

The cited art does not support a conclusion of lack of enablement of the instant claims.

The Office Action asserted that the state of the prior art appears to recognize a high degree of unpredictability in the field of arginine derivatization. In support of this assertion, the Office Action cited the following art: 1) Baburaj et al. ((1994) *Biochim. Biophys. Acta* 1199:253; "Baburaj"); 2) Schwarzenbolz et al. ((1997) *Z. Lebensm. Unters. Forsch. A* 205:121-124; "Schwarzenbolz"); and Sopio and Lederer ((1995) *Z. Lebensm. Unters. Forsch.* 201:381-386; "Sopio").

Baburaj

Baburaj discusses two α-dicarbonyl compounds, designated HOCGO and DMACGO. The Office Action stated that Baburaj found the HOCGO and DMACGO are capable of reacting with cysteine and lysine residues. However, the possibility that HOCGO and DMACGO might be capable of reacting with cysteine and lysine residues has no bearing on a determination of whether the instant claims are enabled. **All that is required is that the α-dicarbonyl compound modify any SDMA and any arginine that may be present in the sample, and that the α-dicarbonyl compound not modify ADMA.** Baburaj states that HOCGO and DMACGO are useful for reacting with arginines. Thus, if anything, Baburaj actually supports the fact that the instant claims are enabled.

Schwarzenbolz

Schwarzenbolz discusses reaction of glyoxal with proteins. The Office Action stated that Schwarzenbolz teaches that under certain conditions, glyoxal produces two arginine derivatives. However, the possibility that glyoxal might produce two arginine derivatives has no bearing on a determination of whether the instant claims are enabled. **All that is required is that the α-dicarbonyl compound modify any SDMA and any arginine that may be present in the sample, and that the α-dicarbonyl compound not modify ADMA.** Schwarzenbolz indicates that glyoxal modifies arginine. Thus, if anything, Schwarzenbolz actually supports the fact that the instant claims are enabled.

Sopio

Sopio discusses reaction of 3-deoxypentosulose with *N*-methyl- and *N,N*-dimethylguanidine as model reagents for protein-bound arginine and for creatine.

The Office Action stated that under certain experimental conditions, deoxyosones result in two tautomeric products; and stated that it is not clear whether these and other derivatives are contemplated, and whether such derivatives are distinguishable from ADMA.

However, the possibility that deoxyosones might produce two tautomeric products has no bearing on a determination of whether the instant claims are enabled. **All that is required is that the α-dicarbonyl compound modify any SDMA and any arginine that may be present in the sample, and that the α-dicarbonyl compound not modify ADMA.** Sopio indicates that arginine reacts with the α-dicarbonyl function of deoxyosones. Thus, if anything, Sopio actually supports the fact that the instant claims are enabled.

Conclusion as to the rejection under 35 U.S.C.§112, first paragraph

Applicants submit that the rejection of claims 1-9 and 15-19 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§112, second paragraph

Claims 1-9 and 15-19 were rejected under 35 U.S.C.§112, second paragraph, as allegedly indefinite.

The Office Action stated that:

1) The phrase "said sample is suspected of containing ADMA and at least one of SDMA and arginine" is inconsistent with the preamble phrase "a sample comprising ADMA, SDMA, and arginine";
2) The phrase "contacting resulting in modification" is indefinite;
3) The recitation of "to produce" is indefinite; and
4) The recitation "said modified SDMA and said modified arginine are distinguishable" is indefinite.

Applicants respectfully traverse the rejection.

Requirement under 35 U.S.C.§112, second paragraph

To comply with the requirement of 35 U.S.C.§112, second paragraph, the claims must set out the subject matter **with a reasonable degree of clarity and particularity**. As set forth in MPEP §2173.02, in reviewing a claim for compliance with 35 U.S.C.§112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art of its scope, in other words, whether the scope of the claim is clear to a person of ordinary skill in the relevant art.

As set forth in MPEP §2173.02, definiteness of claim language must be analyzed in light of:

a) the content of the disclosure of the patent application;
b) the teachings of the prior art; and
c) the claim interpretation that would be given by one possessing the ordinary level of skill in the art at the time the invention was made.

Applicants submit that, as currently pending, claims 1-9 and 15-19 are clear and need not be amended.

Nevertheless, and solely in the interest of expediting prosecution, claim 1 is amended as noted above, which amendments should adequately address the objections raised in the Office Action.

Applicants submit that the rejection of claims 1-9 and 15-19 under 35 U.S.C. §112, second paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

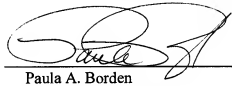
III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-276.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Aug. 2, 2006

By: 
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